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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,436	07/16/2001	Toyomi Kotaki	101136-00021	8485

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Arent Fox Kintner Plotkin & Kahn
Suite 600
1050 Connecticut Avenue N W
Washington, DC 20036-5339

EXAMINER	
YU, MISOOK	
ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 05/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,436	KOTAKI ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *4,6 and 13* is/are allowed.

6)☒ Claim(s) *1-3,5,7-12 and 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Error Report* .

The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Misook Yu.

DETAILED ACTION

Claims 1-17 are pending and examined on merits.

Specification

Compact Disc Submission

The amendment filed 3-20-2003 contains a data file on CD-ROM/CD-R that is unreadable. Applicant is required to resubmit the file(s) in International Standards Organization (ISO) 9660 standard and American Standard Code for Information Interchange (ASCII) format as required by 37 CFR 1.52(e)(3). No new matter may be introduced in presenting the file in ISO 9660 and ASCII format. Therefore the objection of the specification is maintained. Appropriate correction is required. Note the attached Error report. For further assistance on this matter, call the person on the attached Error report.

Claim Rejections - 35 USC § 112

Rejection of claims 1-12 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement **is withdrawn** the Office interprets the limitations "pentapeptide" having SEQ ID NO:1 or "tetrapeptide" having SEQ ID NO:2 as the peptides consisting either SEQ ID NO:1 or SEQ ID NO:2.

Claims **1-3 remain rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession** of the claimed invention. Applicant argues that one skilled in the art would have known the nucleotide of the gene encoding the pentapeptide or tetrapeptide based the triplet codons corresponding to amino acids. However, this argument is not persuasive for two reasons. First, Steveson et al (2003, Endocrinology, vol. 144, pages 188-200) teach that gene does not dictate amidation, which is post-translation process. Second, Darnell et al (1990, Molecular Cell Biology, page 344 only) teach that a gene

comprises all nucleic acid sequences necessary to produce a functional protein or RNA including promoters and enhancers. The specification discloses a penta-, a tetra-peptide but no gene. Peptides of these sizes are usually produced by proteolytic processing of precursor (see Steveson et al above) and there is no description of the precursor, therefore no description of gene encoding it, either. In short, the specification does not teach any gene controlling amidation. Amending the claims to "an isolated and purified nucleic acid molecule encoding SEQ ID NO:1" would obviate this rejection.

Claim Rejections - 35 USC § 102

The art rejection of record **is withdrawn** because applicant argument is persuasive and further a peptide consisting either SEQ ID NO:1 or 2 is free of art.

NEW GROUNDS OF RJECTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 are confusing because the claims appear to say applicant wants to claim a gene encoding an amidated peptide. The art (see Steveson et al above) recognizes that gene does not dictate amidation.

Claims 3 and 5 recite "derived from" but it is not clear what the metes and bounds are for the limitation. Amending the claims to "Extracted from" or "obtained from" would obviate the rejection.

Claims 7-12, and 14-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use

the invention. This rejection is based on the Office interpretation that the claims are drawn to the peptides for the intended use in cancer treatment. Limiting the scope of the claims to composition comprising the peptides and physiologically acceptable carrier would obviate this rejection.

The specification teaches the disclosed peptides controls dormancy state of silk worm and that the peptides causes apoptosis of in vitro cancer cells. Based on the disclosure, the claimed agents are not enabled for cancer treatment because the art recognizes that cancer treatment is not trivial and unpredictable. It is the Office's position that in vitro data could not be extrapolated to what will happen in vivo because it is well known in the art that characteristics of cultured cells generally differ significantly from the characteristics of in vivo primary cancers or metastatic cancers. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and

cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, based on the in vitro data presented in the specification, it could not be predicted that either the pentapetide or the tetrapeptide could kill in vivo cancer cells. In addition, one cannot extrapolate the teaching of the specification to the claimed invention because the specification provides no exemplification of or guidance on how to use the claimed biological cell-control agent for cancer treatment.

It is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para of column 1). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed peptide would be useful for treating cancer. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of

experimental evidence, one skilled in the art would have reason to question the assertion that the claimed peptide would be useful for treating cancer. The specification provides insufficient guidance with regard to theses issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed peptides in killing tumor cells *in vivo* with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success.

Allowable Subject Matter

Claims 4, 6, and 13 are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

Misook Yu
May 23, 2003